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GRAND ROUNDS IN ENVIRONMENTAL MEDICINE

Hypersensitivity Pneumonitis Associated with Environmental Mycobacteria

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Abbreviations with definitions used in the manuscript:

FEV_1 = Forced expiratory volume in 1 second in liters ; FVC = Forced vital capacity in liters; D_LCO = diffusing capacity for carbon monoxide; rest O_2 sat = Oxygen saturation at rest; Exert O_2 Sat = Oxygen saturation with exertion

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Abstract

A previously healthy man working as a machine operator in an automotive factory developed respiratory symptoms. Medical evaluation showed abnormal pulmonary function tests, a lung biopsy showed hypersensitivity pneumonitis, and his illness was traced to his work environment. His physician asked the employer to remove him from exposure to metal working fluids. Symptoms re-occurred when he was later re-exposed to metal working fluids, and further permanent decrement in his lung function occurred. Investigation of his workplace showed that five of six large reservoirs of metal working fluids (cutting oils) grew *Mycobacterium chelonae (or M. immunogenum)*, an organism previously associated with outbreaks of hypersensitivity pneumonitis in auto making factories. His lung function has remained stable with complete removal from exposure. The employer, metal working fluid supplier, union, and the National Institute for Occupational Safety and Health were notified of this sentinel health event. No further cases have been documented in this workplace.

Case Presentation

A 57 year old non-smoking auto parts machine operator presented in 1995 because of shortness of breath on exertion, cough, fatigue and chest congestion. He operated a machine that cut metal parts using a semi-synthetic metal working fluid (figure 1) that was collected and recycled through large tanks holding over one thousand gallons of fluid. A chest radiograph showed a generalized increase in interstitial markings. He was treated with empiric antibiotics on two occasions. Later his treating physician suspected occupational asthma due to exposure to oil mist, and asked the employer to remove him from exposure to metal working fluids. A trial of bronchodilator medications was not effective in improving symptoms, which were worse after work. Spirometry was performed by the medical department at work just before and after a 5 day work week; no change in spirometry was noted. A measurement of total metal working fluid aerosol done in the patient's work area showed that the mass of aerosol was 0.42 milligram (mg) per cubic meter of air sampled, blow the recommended limit of a recent advisory committee.

When the physician's recommendations to remove the patient form all metal working fluids was not followed, and symptoms persisted, he was referred to a pulmonary specialist for further testing. Pulmonary function tests showed a reduced diffusing capacity of 67% predicted with oxygen desaturation on ambulation (Table 1) and a carbachol challenge (a test for airway hyperreactivity in asthma), was negative. Bronchial alveolar lavage showed 90% lymphocytes and 10% macrophages in alveolar lining fluid, with negative smear and culture for acid fast bacilli (mycobacteria) and fungi. A trans-bronchial lung biopsy (Figure 3) showed interstitial chronic inflammation and collections of epithelioid cells suggestive of granulomas with negative stains for acid fast bacilli and fungus and on review diagnostic of hypersensitivity pneumonitis. Testing several years later of the preserved tissue block by polymerase chain reaction was negative for sequences found in *Mycobacterium chelonae.* His treating

pulmonologist suspected the hypersenstivitiy pneumonitis was due to bacteria growing in the metal working fluid. Serum precipitating antibodies to a standard panel of nine substances including bacteria, several fungi, and pigeon serum were all negative. The pulmonologist gave him a brief note for his employer restricting exposure to metal working fluids; the company physician misinterpreted the message as indicating that the patient had chronic obstructive pulmonary disease made worse by metal working fluid exposures, and changed his work location but did not fully restrict him from exposure to metal working fluids.

No specific interventions were made in the workplace with regard to the metal working fluids, although a plant wide program of reduction of fluid aerosol exposures for all workers was already in progress. Several months later the patient had an uncomplicated myocardial infarction, and after three months returned to work with continued exposure to metal working fluids. Three years later, in 2000, he noted daily nasal congestion associated with work, and worsening dyspnea on exertion. His pulmonologist repeated lung function tests which showed a further decline in diffusing capacity to 44% predicted (Table 1), and a thin section CT scan of the chest (Figure 2) showed "ground glass" opacities indicating interstitial lung disease and mild bronchiectasis. A visit to his residence by a treating physician trained in occupational and environmental medicine did not reveal any exposures suggestive of contributing to his hypersensitivity pneumonitis.

With the assistance of the county health department, samples of metal working fluid were obtained for culture from the large reservoir supplying metal working fluids to the patient's work area. Standard bacterial and fungal counts were below the level of detection of 10 organisms per milliliter (mL), unusually low for industrial metal working fluids which are usually contaminated by microorganisms. Stain of the centrifuged fluid pellet for acid fast bacilli was qualitatively "very high" and culture grew 1.6×10^5 mycobacteria per ml, which were identified as *M. chelonae.* (This mycobacterium, though similar to the *M.chelonae-abscessus* Group, has been proposed as a new species, *M. immunogenum).* (Brown-Elliott, 2002). Additional, separate

fluid specimens were sent to another laboratory which cultured and identified the same organism. Samples of fluid from five reservoirs, a blank of "virgin" metal working fluid and a tap water control were for a third time tested and showed greater than 2500 mycobacteria per mL , with single stranded conformational polymorphism analysis showing *M. chelonae* sub-type *immunogenem* in the used fluid samples, and none in the virgin fluid or tap water. Endotoxin, the active agent in the walls of gram negative bacteria, was measured in the five samples from the five reservoirs at from 2.4×10^2 to 2.5×10^4 Endotoxin Units per ml fluid by the limulus assay. Based on these findings, he was removed completely from exposure to metal working fluids.

The treating occupational physician scheduled a meeting with the plant occupational physician, industrial hygienists, and the contracting supplier of the metal working fluids to recommend:

1. a survey of symptoms and chest x-rays of workers exposed to metal working fluids to identify any additional cases
2. testing of all metal working fluid reservoirs in the facility for mycobacteria

In addition, the disease occurrence was reported to the Division of Respiratory Disease Studies of the National Institute for Occupational Safety and Health.

Discussion

Metal working fluids are widely used where metal is cut, drilled, milled, or otherwise shaped with cutting tools to remove heat from both the machine tool and the product being made, to lubricate the parts, remove metal debris, and inhibit metal corrosion. Hypersensitivity pneumonitis is a serious environmental immunologic lung disease in which recurrent exposures to inhaled antigens lead to immunologic sensitization with a predominantly cell-mediated lung response. Subsequent exposures then cause an inflammatory response in the lung which can produce symptoms of dyspnea, cough, and wheeze; fever and elevated blood white count; and transient lung infiltrates and hypoxemia. Persistent disease can cause permanent loss of lung function and even death. Many patients develop disease from exposures associated with work, though exposure to biological aerosols from home can also cause disease (Wright et al.1999; Apostolakos et al. 2001; Kawai et al. 1984).

The condition was first described in dairy farmers exposed to aerosol from stored, moldy hay containing mixed micro-organisms. The list of inhaled substances or mixtures known to cause this condition has grown over the years (Patel, 2001); most (but not all) causative agents are biological materials, including proteins from pigeons and other domestic birds. Blood tests for serum precipitating antibodies to a panel of approximately 10 common causes of hypersensitivity pneumonitis are available from commercial laboratories. However, disease may occur from exposure to substances not included in these panels. In addition, exposure may result in asymptomatic sensitization. Use of precipitating antibodies in diagnosis of hypersensitivity pneumonitis is limited by these factors.

Metal working fluids may be pure petroleum oils (“straight oils”), emulsions of petroleum in a water base (semi-synthetic fluids) or emulsions of synthetic oils in water (synthetic fluids). Because they contain biologically available carbon (in the form of lipids) and water, water-based metal working fluids routinely sustain microbial growth, but excess growth

degrades the fluids and leads to loss of usefulness. Thus, standard usage of these metal working fluids in industry often includes routine testing for bacteria counts (without identification of all organisms) and the use of microbicides with the objective of suppressing, though not necessarily sterilizing, microbial growth.

A variety of respiratory illnesses have been described associated with the occupational inhalation of metal working fluids, including bronchitis, asthma, and lipoid pneumonia (Leigh and Hargreave 1999; Cullen et al. 1981; Kennedy et al.1989), and their toxicity has recently been reviewed (Gordon 2004). Currently there is no specific Occupational Safety and Health Administration (OSHA) standard for metal working fluids, although guidance in prevention of health hazards is provided in a NIOSH Criteria Document (Centers for Disease Control and Prevention, 1998). An advisory panel appointed by OSHA recommended a new permissible exposure limit of 0.4mg/m^3 of thoracic particulate and 0.5 mg/m^3 of total particulate based in large part on the NIOSH Criteria Document. However, this recommendation has not been the subject of rule making as of this writing. Hypersensitivity pneumonitis associated with metal working fluids was first described in 1995 (Bernstein et al. 1995). Since then, numerous outbreaks have been described, associated with inhalation of aerosols of water-containing metal working fluids (reviewed in Kreiss and Cox-Gaenser 1997). Prevention efforts have focused on reduction of inhalation exposures by workplace modifications that reduce generation of aerosols or improve dilution and ventilation of workplace air, and one follow-up study has documented successful remediation (Bracker et al. 2003).

More recently, outbreaks of this condition have been found in workplaces with metal working fluids containing non-tuberculous mycobacteria (Kreiss and Cox-Gaenser 1997; CDC 2002), most frequently *M. immunogenum.,* Detection of these mycobacteria requires special laboratory culture and identification techniques which are not included in routine microbiological testing of industrial metal working fluids, such that their identification requires knowledge of their potential for growth and the ability to perform special testing.

During recent years, association of hypersensitivity pneumonitis disease with a different species, *M. avium complex* (MAC), from hot tubs, whirlpool baths and spas has also been identified, sometimes referred to as 'Hot tub lung' (Rickman et al. 2002). In these hot water bathing tubs, water may be agitated by powerful jets of air or of water that produce bubbles and hence aerosols of water droplets. MAC grows well in the high water temperature of the indoor hot tub. The combination of MAC organisms' growth, and jet aerosolization and subsequent inhalation of large amounts of MAC presumably lead to the development of this disease. 'Hot tub lung' appears to be hypersensitivity pneumonitis to MAC aerosol rather than a direct infection of the lung, though this subject is still a matter of debate (Aksamit 2003, Embil 1997). Interestingly, there have been no documented cases of 'Hot tub lung' with outdoor hot tubs. Pulmonary function tests were mainly restrictive with occasional obstruction. (Anonymous 2000; Kahana and Kay 1997; Khoor et al 2001; Mangione et al 2001; Mery and Horan 2003; Rihawi et al. 2004). Chest radiography shows diffuse infiltrates and high-resolution computed tomography of the chest shows ground glass opacities and micronodules (Pham et al. 2003). Sputum culture was positive for MAC in about 70 % of the patients, transbronchial biopsy and bronchoalveolar lavage cultures increased the yield further. Hot tub water usually grows MAC. The histopathologic findings reveale discrete non-necrotizing granulomas with centrilobular and bronchiolocentric distribution. The granulomas described in this disease were more exuberant and well formed than those seen in typical cases of hypersensitivity pneumonitis from other causes.

There exists no standard approach to treatment of 'Hot tub lung'. Case reports describe significant improvement with removal from exposure to the hot tubs. Oral corticosteroids, anti-mycobacterial therapy or both have also been used. The expected course of this disease following the above measures is recovery without relapse. Measures proposed as being helpful in prevention include better ventilation of the hot tub room , frequent cleaning of the hot tub, frequent change of hot tub water, and use of disinfectants such as chloramines, bromine and

ultraviolet light. These measures are similar to those usually proposed for prevention of hypersensitivity due to exposure to mycobacteria in metal working fluids.

Conclusions

Environmental mycobacteria have been associated with a serious lung condition, hypersensitivity pneumonitis, when inhaled as part of liquid droplet aerosols generated from large volumes of liquids serving as a culture medium. These organisms are found commonly in nature and are able to grow in sufficient quantitites to cause diease. The case reported and discussed here involved an occupational source of such an exposure (aerosolized metal working fluid in a machining environment), although aerosols containing mycobacteria have been described in other settings as well (aerosolized water from hot tubs). For this reason, specific investigation of sources of aerosols in the work or home environment of patients with this condition should consider the growth of mycobacteria as one of the potential sources of disease. As with other causes of hypersensitivity pneumonitis, removal from exposure and remediation of exposure are the first approaches to treatment.

Table 1: Pulmonary Function Laboratory Data

Date	**FEV_1**	**FVC**	**D_LCO**	**Rest** O_2 Saturation	**Exercise** O_2 Saturation	**Notes**
6/85	2.70 (88%)	3.0 (70%)	-	-	-	Pre-placement work exam before onset of symptoms
1/96	2.77 (94%)	3.47 (95%)	-	-	-	After onset of symptoms; spirometry before the work week
1/96	2.98 (101%)	3.40 (93%)	-	-	-	After shift at end of work week
9/97	-	-	-	96%	96%	-
1/98	-	-	(67%)	-	-	-
4/00	2.52 (89%)	3.14 (89%)	9.8 (44%)	92%	89%	More symptomatic
6/00	1.86 (60%)	2.55 (65%)	-	-	-	-
4/04	2.42 (89%)	3.15 (92%)	11.5 (45%)	-	-	Symptoms stable

FEV_1 = Forced expiratory volume in 1 second in liters (percent predicted); FVC = Forced vital capacity in liters (percent predicted): D_LCO = diffusing capacity for carbon monoxide (percent predicted); rest O_2 sat = Oxygen saturation at rest; Exert O_2 Sat = Oxygen saturation with exertion.

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Figure Legends

Figure 1.

Milky appearing metal working fluid is being flowed over auto parts to provide friction reduction and cooling of metal tools. As fluids are sprayed over metal parts, an visible aerosol is formed which can be breathed by operators of the machinery unless specific control measures are instituted. Fluids are recycled from large holding tanks. The presence of carbon and water in fluids permits growth of micro organisms including mycobacteria. This process required resulted in lung disease in the patient described. Photo is of a process similar to that used by the patient,

Figure 2.

Thin section CT scan of the chest showing ground glass opacities in the lung parenchyma, indicating intersitital inflammation and/or fibrosis.

Figure 3.

Trans bronchial biopsy specimen of the lung showing marked alveolar inflammation and cell proliferation with the presence of inflammatory and epithelioid cells.

Figure 1.

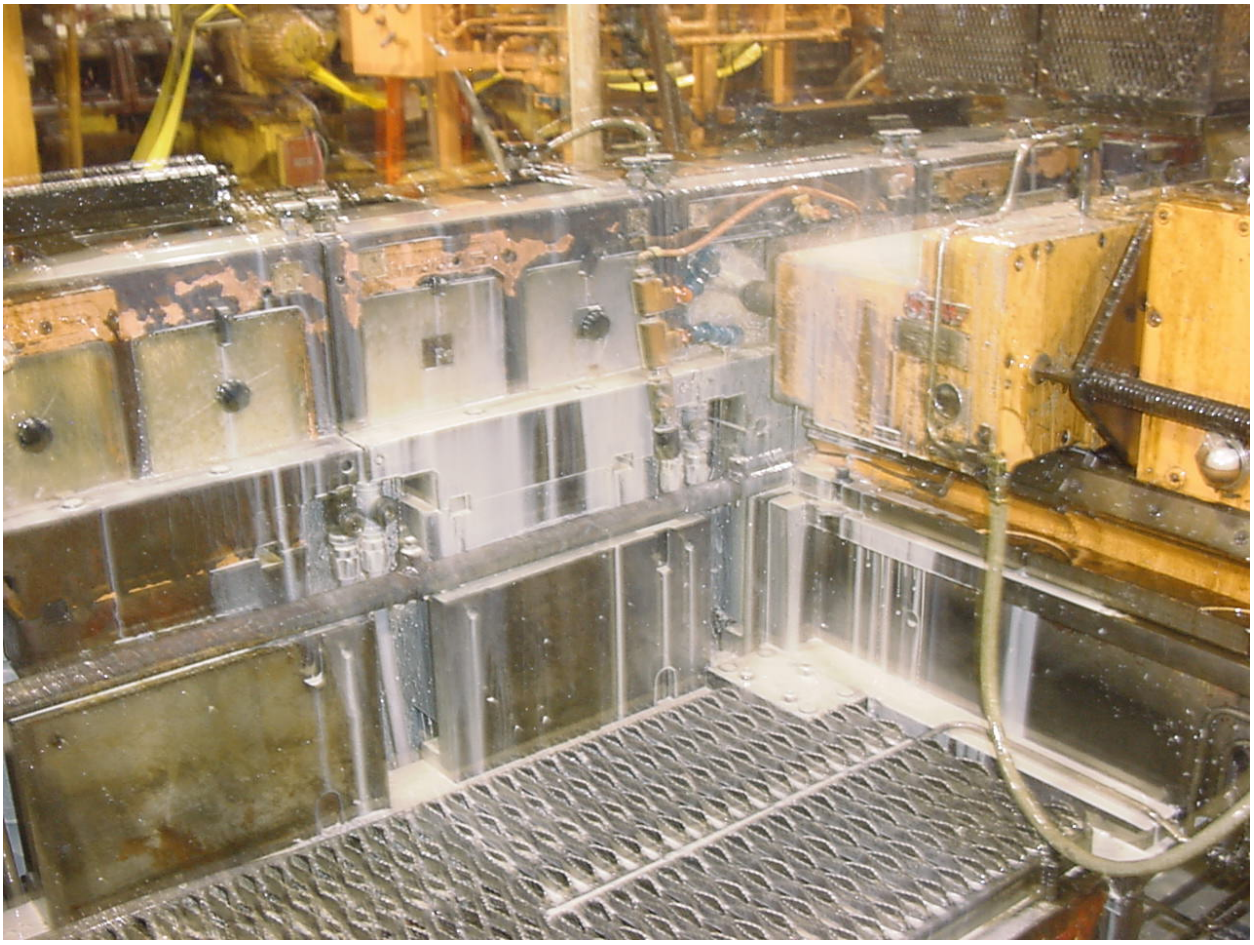

Figure 2.

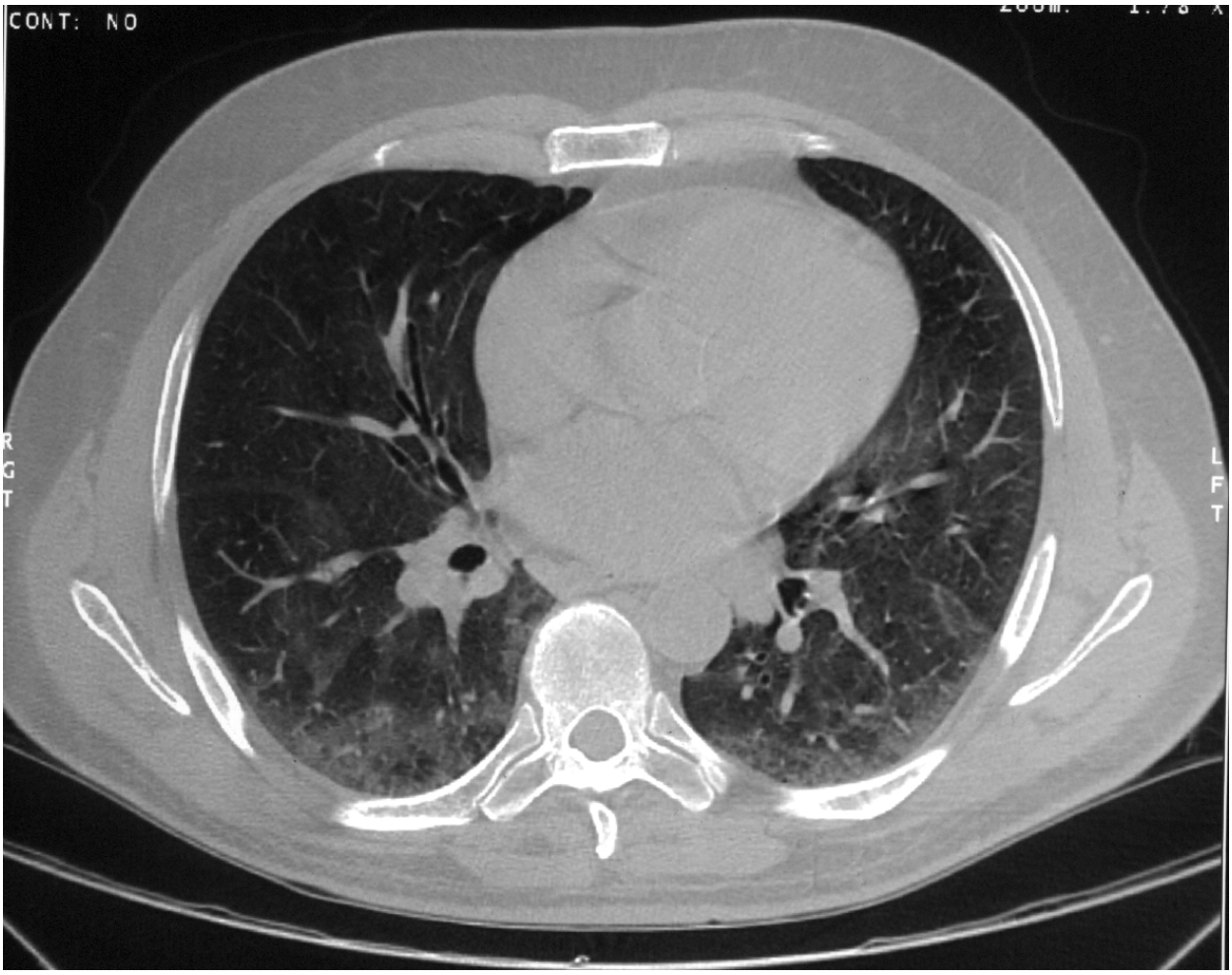

Figure 3.